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(57) Abstract

This invention relates to quinine and quinidine compounds which are ligands, in particular, antagonists, of the Calcitonin Gene-Related Peptide ("CGRP") receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CGRP, including, but not limited to, headaches, especially migraines; non-insulin dependent diabetes mellitus; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinits; and asthma, all in mammals, by the use of quinine and quinidine CGRP receptor antagonists.

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COMPOUNDS AND METHODS

FIELD OF THE INVENTION

This invention relates to quinine and quinidine compounds which are ligands, in particular, antagonists, of the Calcitonin Gene-Related Peptide (hereinafter "CGRP") receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CGRP, including, but not limited to, headaches, especially migraines; non-insulin dependent diabetes mellitus (hereinafter "NIDDM"); cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, all in mammals, preferably humans, by the use of CGRP receptor ligands, in particular, quinine and quinidine antagonists, thereof.

BACKGROUND OF THE INVENTION

CGRP is a 37 amino acid polypeptide that is stored and released from nerve terminals in both the central nervous system and the peripheral nervous system. (Goodman et al., *Life Sci.*, Vol. 38, pp. 2169-2172 (1986)). CGRP has been detected in nerves innervating the heart, peripheral and cerebral blood vessels, and kidneys by immunohistochemical and radioimmunoassay methods. (Yamamoto et al., *Prog. Neurobiol.*, Vol. 33, pp. 335-386 (1989)). CGRP has been shown to mediate its biological response by binding to specific cell surface receptors that have been identified in a variety of tissues. Evidence from biochemical studies suggest that CGRP receptors belong to the family of G-protein coupled receptors. The widespread distribution of CGRP receptors on muscle, glandular, epithelial and neuronal cells is consistent with its wide range of biological actions, including peripheral and cerebral vasodilation (Brain et al., *Nature*, Vol. 313, pp. 54-56 (1985)); cardiac acceleration (Sigrist et al., *Endocrinology*, Vol. 119, pp. 381-389 (1986)); regulation of calcium metabolism (Grunditz et al., *Endocrinology*, Vol. 119, pp. 2313-2324 (1986)); reduction of intestinal motility (Fargeas et al., *Peptides*, Vol. 6, pp. 1167-1171 (1985)); regulation of glucose metabolism, e.g., reduction of insulin secretion and insulin sensitivity, (Hermansen et al., *Peptides*, Vol. 27, pp. 149-157 (1990); and Molina et al., *Diabetes*, Vol. 39, pp. 260-265 (1990)); reduction of appetite and reduction of growth hormone increase (Tannenbaum et al., *Endocrinology*, Vol. 116, pp. 2685-2687 (1985)).

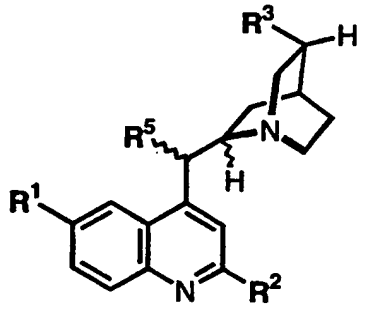
Since CGRP has a number of effects on the cardiovascular, central nervous, gastrointestinal, respiratory and endocrine systems, it has now been discovered that limited and selective inhibition of CGRP receptor mechanisms represents a novel preventative and therapeutic approach to the treatment of a broad variety of disease states that are mediated by CGRP. In particular, the development of an active CGRP receptor antagonist would be expected to be useful in the treatment of a variety of

disease states that are mediated by CGRP including, but not limited to, headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, all in mammals, preferably humans.

Surprisingly, it has now been discovered that a class of non-peptide compounds, in particular quinine and quinidine compounds of formula (I) and formula (IA), several of which have been previously described as being useful in the treatment of malaria (U.S. Patent No. 3,663,552, issued May 16, 1972; and Yardley et al., *J. Med. Chem.*, Vol. 14, No. 1, pp. 62-65 (1971)), also function as CGRP receptor antagonists, and therefore, have utility in the treatment of disease states wherein inhibition of CGRP receptor mechanisms is indicated for prevention or therapeutic treatment thereof.

SUMMARY OF THE INVENTION

In one aspect, the present invention is to a method of treating CGRP mediated disease states, including, but not limited to, headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, all in mammals, preferably humans, comprising administering to such mammal in need thereof, an effective amount of a quinine or quinidine compound of formula (I), or pharmaceutically active salts thereof:



Formula (I)

wherein

R^1 is hydrogen, hydroxy, CO_2R^4 or OR^4;

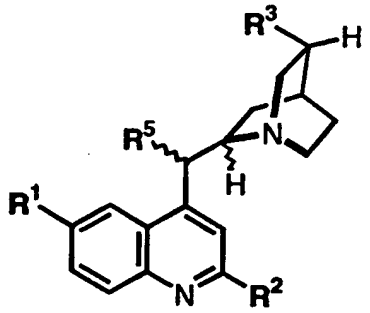
R^2 is phenyl, α or β naphthyl, halophenyl, dihalophenyl, CF_3-phenyl, or optionally substituted phenoxyphenyl;

R^3 is hydrogen, C1 to C4 alkyl, or C2 to C4 alkene;

R^4 is C1 to C4 alkyl; and

R^5 is hydrogen or hydroxy.

In another aspect, the present invention is to a genus of novel compounds of formula (IA), or pharmaceutically active salts thereof, said compounds which are also useful in treating the above-mentioned CGRP-mediated disease states:



Formula (IA)

wherein

R^1 is hydroxy or CO_2R^4;

R^2 is phenyl, α or β naphthyl, halophenyl, dihalophenyl, CF_3-phenyl, or optionally substituted phenoxyphenyl;

R^3 is hydrogen, C1 to C4 alkyl, or C2 to C4 alkene;

R^4 is C1 to C4 alkyl; and

R^5 is hydrogen or hydroxy.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I) or formula (IA) and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are used for treating CGRP-mediated disease states, including, but not limited to headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, all in mammals, preferably humans.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that quinine or quinidine compounds of formula (I) are CGRP receptor ligands, in particular, antagonists thereof. It has also now been discovered that selective inhibition of CGRP receptor mechanisms by treatment with the receptor ligands of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, all in mammals, preferably humans.

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The term "alkene" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethylene, propylene, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "α or β naphthyl" is used herein at all occurrences to describe the point of attachment of the naphthyl moiety to the quinoline ring at position R^2.

The term "halophenyl" is used herein at all occurrences to mean a phenyl moiety that is substituted by a halogen radical as defined above. Suitably, the halogen radical may be positioned on the phenyl moiety ortho, meta or para relative to the quinoline core to which the phenyl is attached.

The term "CF_3-phenyl" is used herein at all occurrences to means a phenyl moiety that is substituted by a trifluoromethyl (-CF_3) radical. Suitably, the trifluoromethyl radical may be positioned on the phenyl moiety ortho, meta or para relative to the quinoline core to which the phenyl is attached.

The term "dihalophenyl" is used herein at all occurrences to mean a phenyl moiety that is substituted by two halogen radicals as defined above. Suitably, one halogen radicals may be positioned on the phenyl moiety ortho, meta or para relative to the quinoline core to which the phenyl is attached. Further, the halogen radicals may be the same or different.

The term "phenoxyphenyl" is used herein at all occurrences to mean a moiety which is represented by the formula "phenyl-oxygen-phenyl". Suitably, one phenyl ring of the phenoxyphenyl moiety is attached ortho, meta or para relative to the quinoline core.

The term "optionally substituted" is used herein at all occurrences to mean that the moieties may or may not be substituted with one to three various functional groups including alkyl, halogen, nitro or trifluoromethyl. It will be understood that the optional substituent(s) may be at a position ortho, meta or para relative to the quinoline core. Preferably, the optional substituent(s) are positioned meta or para relative to the quinoline core.

The term "CGRP mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by Calcitonin Gene-Related Peptide.

As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to, salts with organic acids such as hydrochloric, sulfate, phosphate, diphosphate, hydrobromide and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate and stearate.

For the compounds of formula (I) various embodiments are as follows.

R^1 is suitably hydrogen, hydroxy, CO_2R^4 or OR^4. R^1 is preferably hydroxy or OR^4, more preferably, hydroxy or methoxy.

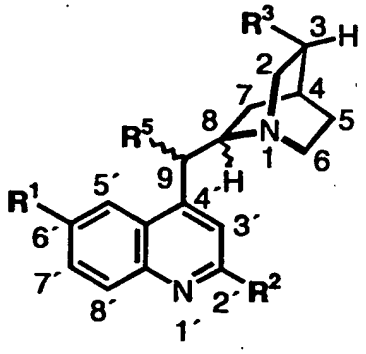
R^2 is suitably phenyl, α or β naphthyl, halophenyl, dihalophenyl, CF_3-phenyl, or optionally substituted phenoxyphenyl. R^2 is preferably halophenyl or phenoxyphenyl.

R^3 is suitably hydrogen, C1-C4 alkyl or C2-C4 alkene. R^3 is preferably hydrogen, methyl or C2 alkene.

R^4 is suitably C1 to C4 alkyl.

R^5 is suitably hydrogen or hydroxy. R^5 is preferably hydroxy.

It will be understood that, according to conventional nomenclature, the difference between a quinine compound of formula (I) or formula (IA) and a quinidine compound of formula (I) or formula (IA) is the stereochemistry at the C8 and C9 positions of the quinine or quinidine molecule. The numbering system used herein is as follows:



The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are within the scope of the present invention. In particular, it will be understood that the C8 and C9 positions of the compounds of formula (I) or formula

(IA) may contain stereocenters. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R).

Among the preferred compounds of the invention are the following compounds:

2'-(4-Chlorophenyl)quinine;
2'-(4-trifluoromethylphenyl)quinine;
2'-(3-trifluoromethylphenyl)quinine;
2'-(4-Chlorophenyl)-10, 11-dihydroquinine;
2'-Phenyl-10, 11-dihydroquinine;
2'-(4-Chlorophenyl)quinidine;
2'-(4-Chlorophenyl)-10, 11-dihydroquinidine;
2'-(4-Chlorophenyl)-10, 11-dihydrocinchonidine;
2'-(4-Chlorophenyl)-6'-hydroxy-10, 11-dihydrocinchonidine;
2'-(4-Chlorophenyl)-10, 11-dihydro-6'-methoxycarbonylcinchonidine; and
2'-(1-Naphthyl)-10, 11-dihydroquinine.

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of formula (I) or formula (IA) ("active ingredient") in an amount sufficient to treat headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion,

soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment of CGRP mediated disease states. Thus, the active ingredient may be administered topically in the treatment or prophylaxis of CGRP mediated disease states, including, but not limited to headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma.

The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The

resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, all in mammals, preferably

humans, which comprises administering to such mammal an effective amount of a CGRP receptor ligand, in particular, an antagonist as depicted in formula (I).

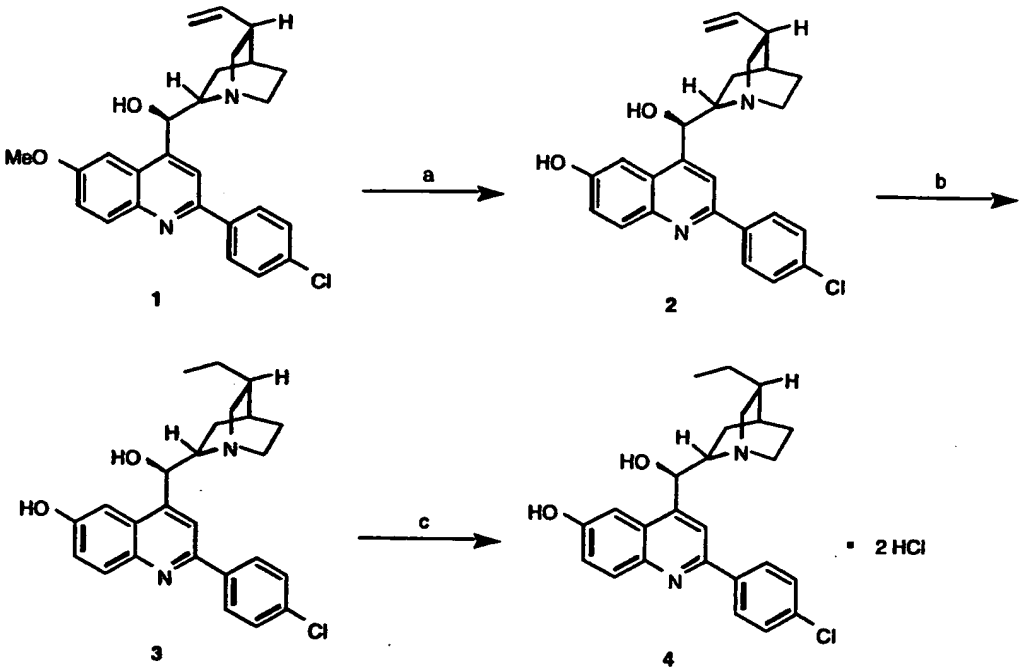
By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) compound is administered to a mammal in need of treatment for headaches, especially migraines; NIDDM; cardiovascular disorders; chronic inflammation; endotoxic shock; arthritis; allergic rhinitis; and asthma, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Methods of Preparation

Scheme 1 (Example 7)

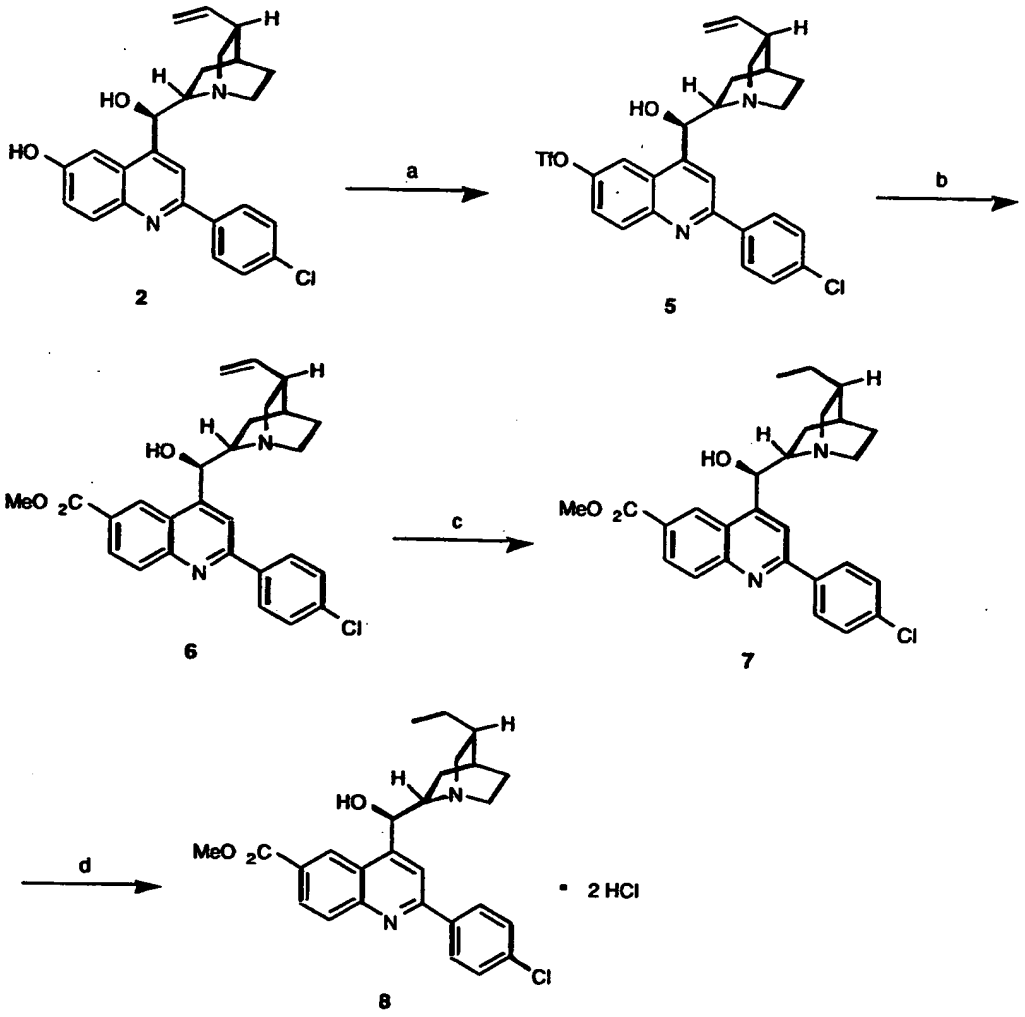


Reagents

(a) BBr_3, CH_2Cl_2, -78 °C -> room temperature ("rt"); (b) H_2, 10% Pd/C, MeOH; (c) 4N HCl/dioxane.

The preparation of 2'-(4-chlorophenyl)-10, 11-dihydrocinchonidine (**3**) and its dihydrochloride salt (**4**, Example 7) proceeded as illustrated in Scheme 1. Starting with 2'-(4-chlorophenyl)quinine (**1**) (made according to Yardley et al., *J. Med. Chem.* **1971**, *14*, pp. 62-65) treatment with boron tribromide (BBr_3) in an inert solvent such CH_2Cl_2 cleaves the 6'-methyl ether providing phenolic compound **2**. Reduction of the 10, 11-double bond using standard catalytic hydrogenation methods yields the saturated analog **3**. If desired, compound **3** can be converted to the dihydrochloride salt **4** via treatment with HCl in an organic solvent such as dioxane.

Scheme 2 (Example 8)



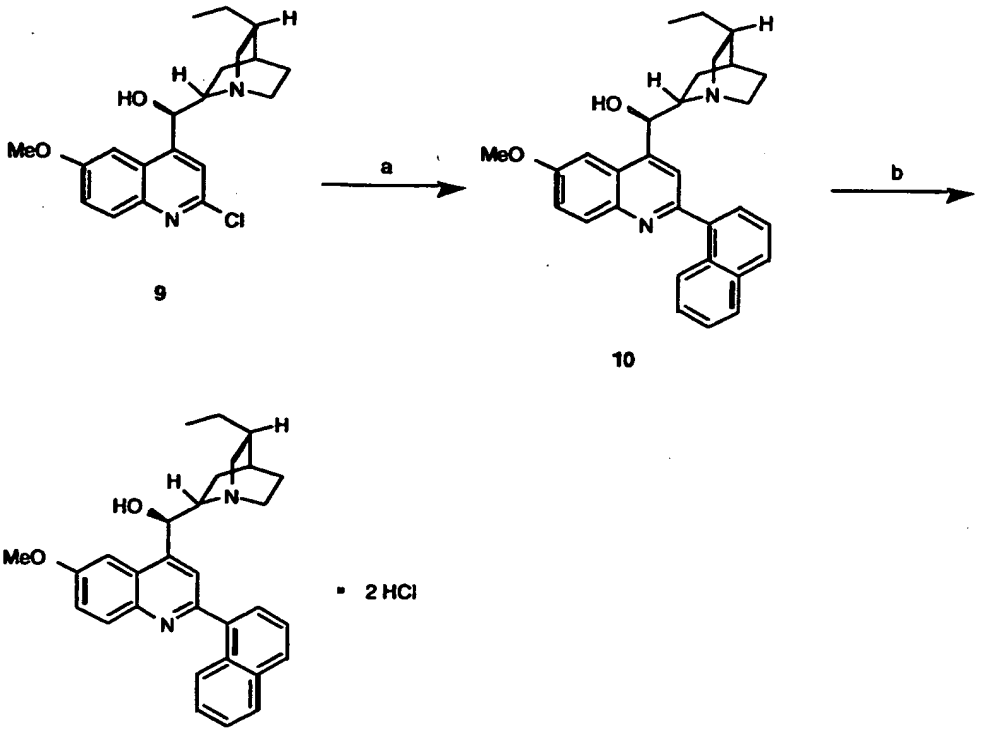
Reagents

(a) NaH, $PhN(Tf)_2$, 0 °C -> rt, THF; (b) 5% $Pd(OAc)_2$, 5% 1, 3-bis(diphenylphosphino)propane ("dppp"), CO, MeOH, Et_3N, DMSO, 70 °C; (c) H_2, 10% Pd/C, MeOH; (d) 4N HCl/dioxane.

The preparation of 2'-(4-chlorophenyl)-10, 11-dihydro-6'-methoxycarbonyl-cinchonidine (7) and its dihydrochloride salt (8, Example 8) are illustrated in Scheme 2. Starting with the previously described 6'-hydroxycinchonidine 2, the 6'-hydroxyl group is converted to the trifluoromethanesulfonate 5 using NaH and N-phenyltrifluoromethane sulfonimide($PhN(Tf)_2$) in a dry aprotic solvent such as THF. This intermediate is then subjected to a Pd-catalyzed carbonylation reaction using MeOH and carbon monoxide at an elevated temperature between 50 - 100 °C. This reaction

is carried out in a polar aprotic solvent such as dimethylsulfoxide ("DMSO") and in the presence of a hindered amine such as triethylamine. The resulting methyl ester **6** is then hydrogenated under standard catalytic hydrogenation conditions to reduce the 10, 11-double bond, thus providing the saturated compound **7**. If desired, compound **7** can be converted to the dihydrochloride salt **8** via treatment with HCl in an organic solvent such as dioxane.

Scheme 3 (Example 9)



Reagents

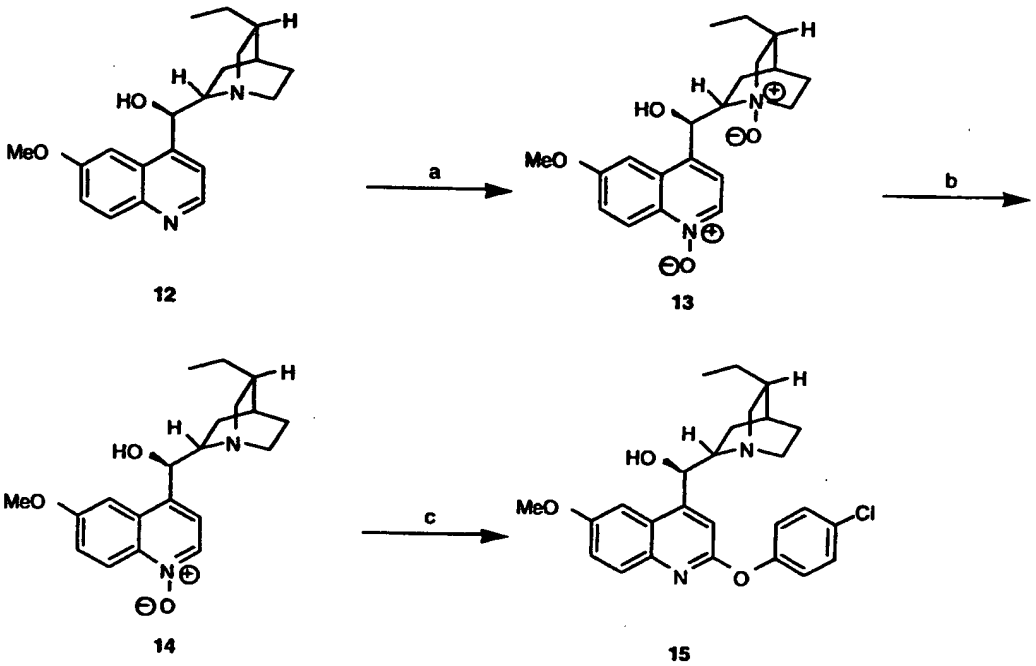
(a) 3% $(CHCl_3)Pd_2(dibenzylideneacetone)_3$, PPh_3, 1-naphthylboronic acid, EtOH, aq. Na_2CO_3, PhH, reflux, 20 h; (b) 4N HCl/dioxane.

An alternative method of preparing 2'-arylquinine derivatives is shown in Scheme 3 using 2'-(1-naphthyl)-10, 11-dihydroquinine dihydrochloride (**11**) as an example (Example 9). The method involves the Pd-catalyzed coupling of arylboronic acids with 2'-chloro-10, 11-dihydroquinine (**9**) made according to Ochiai et al., *Yakugaku Zasshi* **1951**, *71*, pp. 260-262. The arylboronic acids may be purchased from a commercial vendor or prepared by conventional methods from the

corresponding aryl halides. As illustrated for the 1-naphthyl derivative **10**, 1-naphthylboronic acid is coupled to **9** in the presence of a suitable source of Pd^0-catalyst in a alcoholic solvent such as aqueous ethanol using sodium carbonate as a base and running the reaction at a temperature such that the reaction solution is maintained at a gentle reflux. If desired, compound **10** can be converted to the dihydrochloride salt **11** via treatment with HCl in an organic solvent such as dioxane.

One of ordinary skill in the art would recognize that 2'-(4-trifluoromethyl-phenyl)quinine and 2'-(3-trifluoromethylphenyl)quinine are made in a manner analogous to that depicted in Scheme 3 using the appropriate corresponding reagents and starting materials.

Scheme 4 (Example 10)



Reagents

(a) magnesium monoperoxyphthalate, EtOH; (b) SO_2 (gas), $CHCl_3$; (c) 4-chlorophenol, tosyl chloride, triethylamine, CH_2Cl_2, 0 ° C -> rt.

The preparation of 2'-(4-chlorophenoxy)-10, 11-dihydroquinine (**15**, Example 10) proceeded as illustrated in Scheme 4. Starting with commercially available (Aldrich) 10, 11-dihydroquinine (**12**), treatment with a strong peroxy acid causes the oxidation of both nitrogen atoms resulting in the di-N-oxide. The preferred method for accomplishing this transformation is with magnesium

monoperoxyphthalate in absolute ethanol. The di-N-oxide **13** can then be converted to the aryl N-oxide (hereinafter referred to as ar-N-oxide) by selective reduction of the trialkyl amine oxide. This is accomplished by use of a mild reducing agent such a gaseous SO_2. Thus, treatment of **13** in such a manner in an aprotic solvent such as chloroform provides the ar N-oxide **14**. The final conversion is then accomplished by treatment of the ar N-oxide in CH_2Cl_2 with tosyl chloride and triethylamine in the presence of an alcohol. In this example, a phenol is used. Specifically, if 4-chlorophenol is used, phenoxy ether **15** is obtained.

Example 1

Preparation of 2'-(4-chlorophenyl)quinine dihydrochloride

(a) 2'-(4-Chlorophenyl)quinine:

The title compound was prepared according to the experimental disclosures found in U.S. Patent No. 3,663,552, issued June 18, 1974 to Yardley et al., Example 11 (column 14, line 29), and Yardley et al., *J. Med. Chem.* **1971**, *14*, pp. 62-65, Example 18. In particular, the procedure for the preparation of 2'-methylquinidine (on page 65) was followed, except substituting quinine ar-N-oxide for quinidine ar-N-oxide, toluene for benzene, NaOH for KOH, Na_2SO_4 for K_2CO_3, and using 4-chlorophenylmagnesium bromide as the Grignard reagent. Also, instead of recrystallization from methanol, the crude product was purified by flash column chromatography (silica, 5:95:0.5 and 10:90:0.5 methanol-ethyl acetate-ammonium hydroxide). MS (ES) m/e 435.2 $[M+H]^+$.

(b) 2'-(4-Chlorophenyl)quinine dihydrochloride:

A solution of the compound of Example 1(a) (66 mg, 0.15 mmol) in 4N HCl/dioxane was stirred at room temperature for 30 min. The solvent was removed *in vacuo*, and the resulting yellow oil was triturated with diethyl ether to produce a cloudy yellow suspension. After removing the diethyl ether by filtration, the yellow residue was dried under vacuum for 20 h to afford the title compound (55 mg, 69%) as a yellow powder. Anal. ($C_{26}H_{29}O_2N_2Cl_3 \cdot {}^2/_3\ H_2O$) calcd: C, 60.07; H, 5.88; N, 5.39. Found C, 60.14; H, 6.04; N, 5.08.

Example 2

Preparation of 2'-(4-chlorophenyl)-10, 11-dihydroquinine dihydrochloride

(a) 2'-(4-Chlorophenyl)-10, 11-dihydroquinine:

The title compound was prepared according to the experimental disclosures found in U.S. Patent No. 3,663,552, issued June 18, 1974 to Yardley et al., Example 11 (column 14, line 34), and Yardley et al., *J. Med. Chem.* **1971**, *14*, pp. 62-65. In

particular, the procedure for the preparation of 2'-(4-chlorophenyl)dihydroquinidine (on page 65) was followed, except substituting the compound of Example 1(a) for 2'-(4-chlorophenyl)- quinidine. Also, instead of recrystallization from diethyl ether, the crude product was purified by flash column chromatography (silica, 5:95:0.5 and 10:90:0.5 methanol-ethyl acetate-ammonium hydroxide). MS (ES) m/e 437.2 $[M+H]^+$.

(b) 2'-(4-Chlorophenyl)-10, 11-dihydroquinine dihydrochloride:

A solution of the compound of Example 2(a) (96 mg, 0.22 mmol) in 4N HCl/dioxane was stirred at room temperature for 30 min. The solvent was removed *in vacuo*, and the resulting oil was triturated with diethyl ether to produce a cloudy yellow suspension. Upon removal of the diethyl ether by filtration, the yellow residue was dissolved in methanol and concentrated *in vacuo*. The yellow solid obtained was suspended in water (HPLC grade) and lyophilized to afford the title compound (92 mg, 82%) as an amorphous yellow solid. Anal. ($C_{26}H_{31}O_2N_2Cl_3 \cdot 1\ H_2O$) calcd: C, 59.15; H, 6.30; N, 5.31. Found C, 58.93; H, 6.15; N, 5.04.

Example 3

Preparation of 2'-phenyl-10, 11-dihydroquinine dihydrochloride

(a) 2'-Phenyl-10, 11-dihydroquinine:

The title compound was prepared according to the experimental disclosures found in U.S. Patent No. 3,663,552, issued June 18, 1974 to Yardley et al. and Yardley et al., *J. Med. Chem.* **1971**, *14*, pp. 62-65. In particular, the general procedures for preparing 2'-aryldihydroquinidine (on page 65) were followed, except substituting quinine ar-N-oxide for quinidine ar-N-oxide, tetrahydrofuran for benzene, and using phenylmagnesium bromide as the Grignard reagent. Also, instead of recrystallization, the crude product was purified by flash column chromatography (silica, 10:90:3 methanol-methylene chloride-formic acid). ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-8.09 (m, 3H), 7.96 (s, 1H), 7.41-7.49 (m, 3H), 7.33 (dd, J = 6.0 Hz, 1H), 7.17 (d, J = 7 Hz, 1H), 5.57 (d, J = 2 Hz, 1H), 3.88 (s, 3H), 3.40-3.53 (m, 1H), 3.20-3.40 (m, 1H), 3.05-3.11 (dd, J = 25 Hz, 2H), 2.60-2.75 (m, 1H), 2.35-2.45 (m, 1H), 1.80-2.25 (m, 1H), 1.65-1.85 (m, 2H), 1.30-1.55 (m, 2H), 1.15-1.30 (m, 2H), 0.79 (t, J = 19 Hz, 3H).

(b) 2'-Phenyl-10, 11-dihydroquinine dihydrochloride:

A solution of the compound of Example 3(a) (85 mg, 0.2 mmol) in dry methylene chloride (5 mL) was treated with 4N HCl/dioxane (0.5 mL). The solvent was removed at reduced pressure, and the resulting residue was dried under vacuum for 20 h to afford the title compound (96 mg, 92%) as a canary solid. Anal.

($C_{26}H_{32}O_3N_2Cl_3 \cdot 1.5\ H_2O$) calcd: C, 60.23; H, 6.80; N, 5.40. Found C, 60.59; H, 6.86; N, 5.02.

Example 4

Preparation of 2'-(4-chlorophenyl)quinidine dihydrochloride

(a) 2'-(4-Chlorophenyl)quinidine:

The title compound was prepared according to the experimental disclosures found in U.S. Patent No. 3,663,552, issued June 18, 1974 to Yardley et al., Example 4, and Yardley et al., *J. Med. Chem.* **1971**, *14*, pp. 62-65, Example 9. In particular, the procedure for the preparation of 2'-methylquinidine (on page 65) was followed, except substituting toluene for benzene, NaOH for KOH, Na_2SO_4 for K_2CO_3, and using 4-chlorophenyl- magnesium bromide as the Grignard reagent. Also, instead of recrystallization from methanol, the crude product was purified by flash column chromatography (silica, 5:95:0.5 and 10:90:0.5 methanol-ethyl acetate-ammonium hydroxide). MS (ES) m/e 435 $[M+H]^+$.

(b) 2'-(4-Chlorophenyl)quinidine dihydrochloride:

Following the procedure of Example 1(b), except substituting the compound of Example 4(a) (28 mg, 0.065 mmol) for 2'-(4-chlorophenyl)quinine, the title compound (28 mg, 98%) was prepared as a yellow solid. Anal. ($C_{26}H_{29}O_2N_2Cl_3 \cdot 1\ H_2O$) calcd: C, 59.27; H, 5.93; N, 5.32. Found C, 59.55; H, 5.95; N, 5.01.

Example 5

Preparation of 2'-(4-chlorophenyl)-10, 11-dihydroquinidine dihydrochloride

(a) 2'-(4-Chlorophenyl)-10, 11-dihydroquinidine:

The title compound was prepared according to the experimental disclosures found in U.S. Patent No. 3,663,552, issued June 18, 1974 to Yardley et al., Example 11 (Column 14, Line 7), and Yardley et al., *J. Med. Chem.* **1971**, *14*, pp. 62-65, Example 13. In particular, the procedure for the preparation of the title compound (on page 65) was followed. Instead of recrystallization from diethyl ether, the crude product was purified by flash column chromatography (silica, 5:95:0.5 and 10:90:0.5 methanol-ethyl acetate-ammonium hydroxide). MS (ES) m/e 437.2 $[M+H]^+$.

(b) 2'-(4-Chlorophenyl)-10, 11-dihydroquinidine dihydrochloride:

Following the procedure of Example 2(b), except substituting the compound of Example 5(a) (82 mg, 0.188 mmol) for 2'-(4-chlorophenyl)-10, 11-dihydroquinine, the title compound (76 mg, 81%) was prepared as an amorphous yellow solid. Anal. ($C_{26}H_{29}O_2N_2Cl \cdot 1^7/_8\ HCl$) calcd: C, 62.13; H, 6.18; N, 5.57. Found C, 62.16; H, 6.16; N, 5.63.

Example 6

Preparation of 2'-(4-chlorophenyl)-10, 11-dihydrocinchonidine dihydrochloride

(a) 2'-(4-Chlorophenyl)-10, 11-dihydrocinchonidine:

The title compound was prepared according to the experimental disclosures found in U.S. Patent No. 3,663,552, issued June 18, 1974 to Yardley et al., Example 11(Column 14, Line 46), and Yardley et al., *J. Med. Chem.* **1971**, *14*, pp. 62-65. In particular, the general procedures for preparing 2'-aryldihydroquinidine (on page 65) were followed, except substituting cinchonidine ar-N-oxide for quinidine ar-N-oxide, toluene for benzene, NaOH for KOH, Na_2SO_4 for K_2CO_3, and using 4-chlorophenylmagnesium bromide as the Grignard reagent. Also, instead of recrystallization, the crude product was purified by flash column chromatography (silica, 3:97:1, 5:95:1, and 10:90:1 methanol-methylene chloride-formic acid). MS (ES) m/e 407.2 $[M+H]^+$.

(b) 2'-(4-Chlorophenyl)-10, 11-dihydrocinchonidine dihydrochloride:

Following the procedure of Example 2(b), except substituting the compound of Example 6(a) (63 mg, 0.16 mmol) for 2'-(4-chlorophenyl)-10, 11-dihydroquinine, the title compound (63 mg, 78%) was prepared as a light yellow solid. Anal. ($C_{25}H_{29}ON_2Cl_3 \cdot 1^3/_4\ H_2O$) calcd: C, 58.72; H, 6.41; N, 5.48. Found C, 58.72; H, 6.18; N, 5.33.

Example 7

Preparation of 2'-(4-chlorophenyl)-6'-hydroxy-10, 11-dihydrocinchonidine dihydrochloride

(a) 2'-(4-Chlorophenyl)-6'-hydroxycinchonidine:

The compound of Example 2(a) (250 mg, 0.57 mmol) was dissolved in dry methylene chloride (2.7 mL) and cooled to -78 °C in a dry ice/acetone bath. BBr_3 (2.1 mL, 2.3 mmol, 1.1M solution in methylene chloride) was added dropwise to the stirred solution over 10 min. After stirring at -78 °C for 1 h, the reaction mixture was gradually warmed to room temperature and stirred for an additional 20 h. Water was cautiously added to decompose the excess BBr_3, and the reaction mixture was made basic (pH 11-12) with 10% NaOH. The reaction mixture was extracted with methylene chloride (2x), and the organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash column chromatography (silica, 5:95:1 and 10:90:1 methanol-ethyl acetate-ammonium hydroxide). The fractions containing the title compound were concentrated *in vacuo*, and the resulting oil was dissolved in methylene chloride and washed with water. The organic layer was dried (Na_2SO_4)

and concentrated *in vacuo* to afford the title compound (116 mg, 48%) as an orange-yellow powder. MS (ES) m/e 421.2 $[M+H]^+$

(b) 2'-(4-Chlorophenyl)-6'-hydroxy-10, 11-dihydrocinchonidine:

To a solution of the compound of Example 7(a) (115 mg, 0.27 mmol) in dry methanol (1.3 mL) was added 10% Pd/C (12 mg). The resulting mixture was stirred under a hydrogen atmosphere (double-walled balloon pressure) for 2 h. The reaction mixture was diluted with methylene chloride and filtered through Celite®. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (silica, 5:95:1, 10:90:1, and 15:85:1 methanol-ethyl acetate-ammonium hydroxide). The fractions containing the title compound were concentrated *in vacuo*, and the resulting oil was dissolved in methylene chloride and washed with water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound (97 mg, 85%) as a light orange solid. MS (ES) m/e 423.6 $[M+H]^+$.

(c) 2'-(4-Chlorophenyl)-6'-hydroxy-10, 11-dihydrocinchonidine dihydrochloride:

Following the procedure of Example 1(b), except substituting the compound of Example 7(b) for 2'-(4-chlorophenyl)quinine, the title compound was prepared as a yellow solid. Anal. ($C_{25}H_{27}ON_2Cl \cdot 2^1/_2\ HCl \cdot {}^1/_4\ H_2O$) calcd: C, 57.90; H, 5.83; N, 5.40. Found C, 57.74; H, 5.43; N, 5.29.

Example 8

Preparation of 2'-(4-chlorophenyl)-10, 11-dihydro-6'-methoxycarbonylcinchonidine dihydrochloride

(a) 2'-(4-Chlorophenyl)-10, 11-dihydro-6'-trifluoromethylsulfonylcinchonidine:

To a cooled (0°C) solution of the compound of Example 7(b) (46 mg, 0.11 mmol) in dry tetrahydrofuran (0.5 mL) was added NaH (6 mg). After stirring the reaction mixture for 5 min., N-phenyltrifluoromethane sulfonimide (59 mg, 0.17 mmol) was added, and the resulting mixture was stirred at 0 °C for 2 h and at room temperature for an additional 2 h. The reaction mixture was diluted with methylene chloride and washed with 10% HCl, water, and brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash column chromatography (silica, 1:99 and 3:97 methanol-methylene chloride) to afford the title compound (43 mg, 72%) as an off-white solid. MS (ES) m/e 555 $[M+H]^+$.

(b) 2'-(4-Chlorophenyl)-10, 11-dihydro-6'-methoxycarbonylcinchonidine:

A mixture of the compound of Example 8(a) (43 mg, 0.08 mmol), palladium acetate (1 mg, 5 mmol%), 1, 3-bis(diphenylphosphino)propane (1.6 mg, 5 mmol%),

triethylamine (0.03 mL), and methanol (0.4 mL) in dry dimethylsulfoxide (0.5 mL) was purged with carbon monoxide for 5 min. and stirred under a carbon monoxide atmosphere (double-walled balloon pressure) at 70 °C for 20 h. The reaction mixture was diluted with methylene chloride and washed with 10% HCl, water, and brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash column chromatography (silica, 3:97:1 and 5:95:1 methanol-ethyl acetate-ammonium hydroxide). The fractions containing the title compound were concentrated *in vacuo*, and the resulting oil was dissolved in methylene chloride and washed with water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound (15 mg, 40%) as a colorless solid. MS (ES) m/e 465.2 $[M+H]^+$.

(c) 2'-(4-Chlorophenyl)-10, 11-dihydro-6'-methoxycarbonylcinchonidine dihydrochloride:

Following the procedure of Example 2(b), except substituting the compound of Example 8(b) for 2'-(4-chlorophenyl)-10, 11-dihydroquinine, the title compound was prepared as an amorphous maize solid. Anal. ($C_{27}H_{31}O_3N_2Cl_3 \cdot 1^3/_8\ H_2O$) calcd: C, 57.63; H, 6.05; N, 4.98. Found C, 57.38; H, 5.66; N, 4.85.

Example 9

Preparation of 2'-(1-naphthyl)-10, 11-dihydroquinine dihydrochloride

(a) 2'-Chloro-10, 11-dihydroquinine:

The title compound was prepared according to the experimental disclosure found in Ochiai et al., *Yakugaku Zasshi* **1951**, *71*, pp. 260-262. In particular, the experimental procedure for preparing the title compound (on page 261) was followed. MS (ES) m/e 361.2 $[M+H]^+$.

(b) 2'-(1-Naphthyl)-10, 11-dihydroquinine:

A solution of tris(dibenzylideneacetone)dipalladium ($CHCl_3$) adduct (27 mg, 0.026 mmol) in benzene (2.1 mL) in a dry, oxygen-free flask was treated with triphenylphosphine (28 mg, 0.10 mmol). After 15 min. of stirring, the compound of Example 9(a) (310 mg, 0.85 mmol) and 1-naphthylboronic acid (160 mg, 0.94 mmol) was added to the solution. This was followed by the addition of ethanol (0.29 mL) and 2M aqueous sodium carbonate (0.95 mL). The resulting solution was stirred for 20 h under a gentle reflux. The reaction was diluted with water and methylene chloride. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and purified by Chromatotron (methylene chloride and 96:4:1 methylene chloride-methanol-formic acid). The fractions containing the title compound were concentrated *in vacuo*, and the resulting oil was dissolved in methylene chloride and washed with aqueous sodium bicarbonate solution. The organic layer was dried (Na_2SO_4) and

concentrated *in vacuo* to afford the title compound (301 mg, 85%) as a glassy foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.20 (m, 2H), 7.78-7.96 (m, 3H), 7.68 (d, J = 17 Hz, 1H), 7.32-7.60 (m, 3H), 7.20-7.30 (m, 2H), 5.65 (s, 1H), 3.87 (s, 3H), 3.40-3.60 (m, 2H), 3.15-3.20 (m, 1H), 3.05-3.11 (dd, J = 25 Hz, 2H), 2.60-2.75 (m, 1H), 2.35-2.45 (m, 1H), 1.80-2.25 (m, 1H), 1.65-1.85 (m, 2H), 1.30-1.55 (m, 2H), 1.15-1.30 (m, 2H), 0.79 (t, J = 19 Hz, 3H).

(c) 2'-(1-Naphthyl)-10, 11-dihydroquinine dihydrochloride:

Following the procedure of Example 3(b), except substituting the compound of Example 9(b) (301 mg, 0.67 mmol) for 2'-(4-phenyl)-10, 11-dihydroquinine, the title compound (337 mg, 96%) was prepared as a yellow crystalline solid. Anal. ($C_{30}H_{34}O_2N_2Cl_2 \cdot 1\frac{1}{2} H_2O$) calcd: C, 65.21; H, 6.75; N, 5.07. Found C, 65.6; H, 6.69; N, 4.66.

Example 10

Preparation of 2'-(4-chlorophenoxy)-10, 11-dihydroquinine

(a) 10, 11-Dihydroquinine ar N-oxide:

10, 11-Dihydroquinine (hydroquinine, Aldrich; 10 g, 0.030 mol)) was dissolved in absolute ethanol (100 mL) and treated with magnesium monoperoxyphthalate (35 g, 0.057 mol) in two portions. The reaction mixture was stirred at rt for 24 h. The ethanol was removed *in vacuo* and the residue was treated with $CHCl_3$ (100 mL) and H_2O (100 mL). The product was extracted into $CHCl_3$ and the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine and dried (Na_2SO_4). Filtration and evaporation provided 10, 11-dihydroquinine di-N-oxide as a pale yellow foam that was used without further purification.

The crude di-N-oxide obtained above was dissolved in $CHCl_3$ (100 mL) and placed in an ice-H_2O bath. Gaseous SO_2 was bubbled through the solution for 40 min, the reaction flask was then capped and allowed to stir at rt for 18 h. The reaction solution was carefully poured into sat. aq. $NaHCO_3$. The product was extracted into $CHCl_3$ and the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine and dried (Na_2SO_4). Filtration and evaporation provided a dark yellow foam. The crude product was dissolved in hot ethyl acetate - methanol. Upon cooling, crystallization did not take place. The solution was then poured into anhydrous diethyl ether and allowed to sit. The non-crystalline precipitate was collected and dried providing 10, 11-dihydroquinine ar N-oxide (4 g, 40%, two steps) in approximately 90% purity. MS (ES) m/e 343.2 $[M+H]^+$.

(b) 2'-(4-Chlorophenoxy)-10, 11-dihydroquinine:

10, 11-Dihydroquinine ar N-oxide (51 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (0.5 mL), cooled to 0 °C, and treated with 4-chlorophenol (20 mg, 0.30 mmol) and tosyl chloride (36 mg, 0.19 mmol). Triethylamine (0.05 mL, 0.36 mmol) was slowly added to the reaction solution and stirring was continued at 0 °C for 20 min followed by an additional 18 h at rt. The reaction solution was diluted with $CHCl_3$ and washed with 5% Na_2CO_3 and brine and dried (Na_2SO_4). The crude product was purified by flash column chromatography (silica, 5:94:1, 7:92:1, and 10:89:1 methanol-ethyl acetate-NH_4OH). Evaporation of desired fractions yielded a colorless oil. Treatment of the oil with anhydrous methanol provided the title compound as a colorless solid (22 mg, 32%). (ES) m/e 453.2 $[M+H]^+$.

Effect of Compounds on the CGRP Receptor

The test compounds were assayed for the inhibition of [^{125}I] CGRP (obtained from Amersham, Chicago, IL) binding and CGRP-mediated cAMP formation in human neuroblastoma cells (SK-N-MC).

SK-N-MC cells were obtained from American Type Culture Collection (Rockville, MD) and grown in Minimum Essential Media ("MEM") medium containing fetal calf serum (10%). Cells were grown in T-150 flasks or Costar multiwell plates (24 well) and maintained at 37 °C in a 90% humidified incubator with an atmosphere of 5% CO_2 and 95% air.

[^{125}I] CGRP Binding assay:

SK-N-MC cells were homogenized in 5 mM Tris-HCl pH 7.4, 10 mM Na-EDTA and the homogenate was centrifuged at 48,000 g for 20 min at 4 °C. The pellet was resuspended in 20 mM Na-HEPES pH 7.4, 10 mM $MgCl_2$ and recentrifuged as above. The membrane pellets were resuspended in the same buffer and stored frozen at -70 °C. The protein concentration was measured by the Pierce BCA method using bovine serum albumin as the standard.

The [^{125}I] CGRP receptor binding assay was performed using a buffer containing 20 mM Na-HEPES pH 7.4, 10 mM $MgCl_2$, 0.05% BSA and 0.1 mg/mL bacitracin. The membranes (50 ug protein/mL) were incubated with various concentrations (1, 10, 30, 60 and 100 uM) of the test compounds and 40 pM [^{125}I] CGRP in a total volume of 500 uL. for 60 min at 25 °C. The reaction was terminated by addition of 2 mL ice-cold 0.9% NaCl, followed by rapid filtration through Skatron Filtermates presoaked in 0.5% polyethylenimine PEI). The filters were rinsed twice

with 2 mL of cold 0.9% NaCl and the radioactivity counted in a gamma counter. All binding data was analyzed by computer assisted LIGAND 2 program.

CGRP-Mediated cAMP formation:

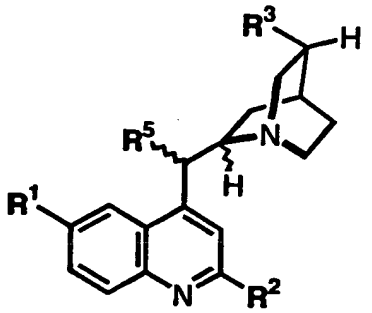
SK-N-MC cells grown in Costar multiwell plates (24 well) were washed with 1 mL phosphate-buffered saline and then 450 uL of fresh buffer supplemented with 0.5 mM isobutylmethylxanthine. Various concentrations (10 uL) of the test compounds were added to the wells and incubated for 30 min at room temperature. Then, 50 uL of 10 nM hCGRP was added and incubated for 10 min at 37 °C. The incubation was stopped by adding 50 uL of ice cold 100% tricholoroacetic acid to each well and cAMP was measured by RIA as explained by Nambi *et al.*, *JPET* **1986**, *237*, 143.

The compounds of this invention show binding activity as CGRP receptor ligands, in particular, as antagonists thereof, and have IC_{50} values in the range of 0.001 to 100 μM. The structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are ligands of the CGRP receptor and which bind thereto with an IC_{50} value in the range of 0.001 to 100 μM.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of treating a CGRP-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein

R^1 is hydrogen, hydroxy, CO_2R^4, or OR^4;

R^2 is phenyl, α or β naphthyl, halophenyl, dihalophenyl, CF_3-phenyl, or optionally substituted phenoxyphenyl;

R^3 is hydrogen, C1 to C4 alkyl, or C2 to C4 alkene;

R^4 is C1 to C4 alkyl; and

R^5 is hydrogen or hydroxy.

2. The method as claimed in claim 1 wherein the compound of formula (I) is a compound selected from:

2'-(4-Chlorophenyl)quinine;

2'-(4-trifluoromethylphenyl)quinine;

2'-(3-trifluoromethylphenyl)quinine;

2'-(4-Chlorophenyl)-10, 11-dihydroquinine;

2'-Phenyl-10, 11-dihydroquinine;

2'-(4-Chlorophenyl)quinidine;

2'-(4-Chlorophenyl)-10, 11-dihydroquinidine;

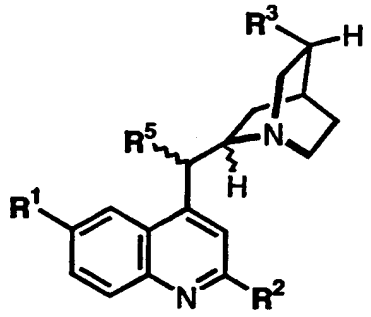
2'-(4-Chlorophenyl)-10, 11-dihydrocinchonidine;

2'-(4-Chlorophenyl)-6'-hydroxy-10, 11-dihydrocinchonidine;

2'-(4-Chlorophenyl)-10, 11-dihydro-6'-methoxycarbonylcinchonidine; and

2'-(1-Naphthyl)-10, 11-dihydroquinine.

3. A compound of formula (IA) or a pharmaceutically acceptable salt thereof:



Formula (IA)

wherein

R^1 is hydroxy or CO_2R^4;

R^2 is phenyl, α or β naphthyl, halophenyl, dihalophenyl, CF_3-phenyl, or optionally substituted phenoxyphenyl;

R^3 is hydrogen, C1 to C4 alkyl, or C2 to C4 alkene;

R^4 is C1 to C4 alkyl; and

R^5 is hydrogen or hydroxy.